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Review

Role of specialized nutrition for wound healing: a narrative review

Angelo Cianciulli[1], Alessandro Delli Poggi[2,3], Noemi Giannetta[3], Massimo Fiorinelli[1], Emanuela Taraborelli[1], Antonella Roncone[1], Raissa Biasiucci[1], Mariachiara Figura[1], Emanuele Di Simone[3], Marco Di Muzio[4]

[1] Sapienza University of Rome, Italy; [2] Department of Surgical Sciences University of Rome 00185, Italy; [3] Department of Biomedicine and Prevention, Tor Vergata University of Rome, 00173 Italy; [4]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Italy - E-mail: marco.dimuzio@uniroma1.it

Summary. *Background.* Wound healing is a dynamic process that depends not only on the interaction between different cellular factors involved in the tissue repair process but can also be adjuvant by a daily nutritional support. Therefore it can be considered a kind of specialized nutrition of which several elements favour the repair and wound healing process. *Objective:* The aim of this study was to verify the effect of beta-hydroxy-beta-methylbutyrate (HMB). To investigate the effects of the combination of arginine, beta-hydroxy-beta-methylbutyrate and glutamine in order to favour collagen deposition on the wound bed. *Materials and Methods:* The research was conducted by analysing publications of recent years and also by setting "title and abstract" as a search criterion. *Results:* From the studies conducted, it was shown that by analysing the combined action of the amino acid mixture in relation to collagen deposition in humans, in just two weeks the integration with arginine, HMB and glutamine produced a significant increase in plasma levels of arginine and ornithine equal to 67%. *Conclusions:* HMB increases lean mass, improves muscle strength and exerts anti-catabolism. Glutamine is essential in the metabolism of lymphocytes, enterocytes and other cells with a rapid turnover. Collagen synthesis and scar formation are necessary for complete resolution of a wound.

Key words: leucine, sarcopenia, HMB, supplements, specialized nutrition

Introduction

Wound healing and nutrition have a strong relationship that has been recognized by physicians and nurses. The critical role of nutrition to healing has been recognized since the beginning of medicine whit Hippocrates (1). Subsequently, several authors such as Coleman, Shaffer, and DuBois (2) or Cuthbertson (3) have analyzed the role of nutrition in wound healing. In the 1930s, Ravdin (4) showed the importance of a good nutritional intake to improve body's ability to heal wounds. Interest has since swung from understanding the basic physiologic mechanisms of wound healing which relies on collagen synthesis, and nutrients such as arginine (Arg) and glutamine (Gln), which promote collagen synthesis (5-7). Before to investigate how wound healing is affected by supplementation with amino acids (Arg, Glu, HMB), it is necessary understand its basic physiological mechanism.

In fact, wound healing involves a complex interaction between epidermis and dermis cells, extracellular matrix, and plasma-derived proteins. All of these components are regulated by a series of signaling molecules, such as cytokines and growth factors (8). This dynamic process is classically divided into three overlapping phases: inflammation, proliferation (also known as replication and synthesis stage) and remodelling of the extracellular matrix (9,10).

This process requires a complex pathway of biochemical reactions and cellular events, secreted growth factors, and cytokines and it also depends on an adequate energizing supplement of protein (essential amino acids), vitamins and the presence of zinc Ions (11). Sherman et al. (12) describe in each stage of wound healing the specific cellular and humoral processes and the respective macro- and micronutrient involvement (Table 1).

It's obvious that nutrition status affects the outcome of the healing process (13). So, the health professionals have to study to recognise the importance of nutritional assessment and management. This multidisciplinary process is classically based on:

- Evaluation of nutritional status;
- Clinical assessment of altered nutritional requirements;
- Implementing best practice in multidisciplinary nutritional care (14).

Table 1. Biochemical and functional pathways utilised during the wound healing process (12)

Macro- and micronutrients	Inflammation	Proliferation
Protein and energy	Increased need for acute phase proteins and proliferation of neutrophils, lymphocytes and macrophages	Increased need for collagen and extracellular-matrix proteins (collagen, elastin), angiogenesis, fibroblast and epithelial proliferation
Arginine	Nitric oxide synthase: permeability, vasodilatation, cytotoxic	Arginase I and II: collagen formation and cell growth
Glutamine	Acute phase protein synthesis, immune cell energy source, DNA replication, phagocytosis, superoxide and glutathione formation antigen presentation	Preferred energy source for fibroblasts
Vitamin C	Antioxidant, chemotaxis	Prolyl and lysyl hydroxylases
Zinc and copper	B and T lymphocyte and neutrophil proliferation, protein synthesis and superoxide dismutase	Epithelialisation and granulation tissue formation
Iron	Immune response, catalase	Prolyl and lysyl hydroxylases

Nutrition screening and assessment

For patients with particular metabolic problems, severely malnutrition problems or a particular stage of illness associated with a state of altered nutrition, Nutritional Assessment (nutritional screening) is performed by an experienced nutrition team (15).

Traditionally, the standard of good practice for the treatment of wounded patients was to review albumin at the blood level as a measure of nutrition or malnutrition. Evaluation of laboratory values is only part of the nutritional evaluation process and must be considered together with other factors. It is essential to carry out an initial assessment of the patient's condition that considers all aspects of the body and lifestyle: daily food / fluid intake, changes in weight status; it is also necessary to pay attention to previous diagnoses, medications, and clinical improvement of the wound (16).

Despite of this, the health professionals have several nutritional screening tools to evaluate nutritional status of patient. These tools differ in scope (17) (Table 2).

Table 2. Nutritional screening tools (17)

Screening assessments	Source, year	Assessment parameters
Maastricht Index	Kuzu et al., 2006	BMI, albumin, prealbumin, and total lymphocyte count
Malnutrition Universal Screening Tool (MUST)	Malnutritional Advisory Group, UK, 2003	Includes BMI, weight loss, acute disease
Mini-Nutritional Assessment-Short Form (MNA-SF)	Rubenstein et al, 2001	Includes recent intake, weight loss, mobility, acute disease, physiological stress, BMI
Subjective Global Assessment (SGA)	Detsky et al., 1987	Medical History and physical examination, Includes weight, intake, GI symptoms, fuctional capacity
Prognostic Nutritional Index (PNI)*	Dempsey et al.	Calculated based on the serum albumin concentration and peripheral blood lymphocyte count

**For the alternative calculation, retinal binding protein was substituted for albumin. This value was called the Burton Inflammatory and Nutritional Index (BINI).*

Implementing best practice in multidisciplinary nutritional care

Based on these tools, the health professionals can implement best practice in nutritional care to improve wound healing. In any case, the recommended daily allowances (RDA) for nutrients are based on the requirements of a healthy population (17); as such, the added demands for wound healing often exceed the RDA.

Despite of this, in well-nourished patients, healing occurs in a short time and with less risk of complications (18). The standard nutritional requirement for the treatment of ulcers, for example, consist of calories, proteins, liquids and some vitamins and minerals (11). Based on the Daily Value (DV) of healthy adults, the recommended amount is 0.8 g protein / kg body weight. Elderly patients may require a higher protein intake of 1g / Kg. (19). Carbohydrate and fat intake is designed to meet basal energy requirements, thus avoiding the use of proteins as an energy source (13). Liquid intake is indispensable as it compensates for the losses caused by tissue damage and the production of exudates (8).

However, despite of the implementing of standard nutritional strategies, this may not be entirely effective for wound healing, due to specific nutritional deficiencies (20).

For this reason, *specialized nutrition* is often used which contains particular nutrients that have the task of encouraging the cicatrisation process (21). Scientific evidence is available regarding the combination of HMB, arginine and glutamine to aid healing, increase protein synthesis by reducing degradation, promoting immune system activity and reducing lean mass loss (22). The present review aimed to assess the efficacy of adjunctive administration of nutritional supplements to propel the wound healing process.

Materials and Methods

We carried out a literature review of studies which aim was to analyse the relationship between nutrition, the use of arginine, β-hydroxy-β-methyl-butyrate (HMB) and glutamine combination specially, and wound healing. The reviewers serarched the bibliographic databased Pubmed, Cochrane and Cinahl for all English language articles between 2006 and August 2016. To obtain an exhaustive string search, through Boolean operators AND and OR, the following keywords were combined: *Leucine; Sarcopenia; HMB; Supplements; Specialised Nutrition*.

Eligibility criteria have been established to define the inclusion or exclusion of studies.

The inclusion criteria for final analysis were as follows reviews published over the past 10 years, clinical trials published in the last 5 years available in full-text, human-related and journalistic articles published in nursing journals. Specific websites such as the American Nurses Association and the European Pressure Ulcer Advisory Panel (EPUAP) were consulted.

Each citation found in the databases (65 citations) was reviewed independently by authors via a title-first approach to obtain records for the abstract screening, according to an inclusion and exclusion criteria decided beforehand.

Irrelevant articles were excluded with respect to the title (17 citations) and the abstract (14 citations), as the suitable results were analysed by reading the full-text (34 citations). By reading the full-text, studies did not focus on the nutrition and wound healing have been excluded.

Results and Discussion

The evidence that nutritional deficiencies are a risk factor for wound healing process has encouraged research and marketing focused on nutritional intervention. Amino acids such as arginine and glutamine play an important role in wound healing process and its combination with HMB is very useful.

The specific role of Arginine and Glutamine in wound healing process

Arginine is a conditioning essential amino acid. In normal physiological conditions it is produced by the body in sufficient quantities but at the same time, in restorative processes, food supplementation becomes necessary (23).

Glutamine is the most abundant amino acid in the human body, carrying out many metabolic functions (13). It is essential during the phases of rapid tissue growth in particular during the healing of a

wound (20). Glutamine acts as an essential substrate for enterocytes, decreasing protein synthesis in skeletal muscle and deficient immune cells (24).

Glutamine and arginine also serve as a metabolic substrate for immune system cells, thus improving the immune function required to prevent or counter infections that may otherwise complicate healing (25,26), as well as the important impact that hand washing has on reducing the transmission of infections (27).

HMB is a leucine metabolite belonging to the branched amino acid family, along with valine and isoleucine (28). They play a significant role in maintaining the nitrogen balance in adults, especially in conditions such as sepsis, trauma and burns (29). HMB is able to inhibit muscle proteolysis and modulate protein turnover (30) (Table 3).

Mixture of Arginine, Glutamine and β-HMB

The present review focuses on the effects of the mixing of more amino acids in relation to the deposition of collagen in humans in order to help early re-epithelialisation of the wound bed and improve cicatrisation. The literature consulted highlights the efficacy of the combination of arginine, HMB and glutamine, with the aim of stimulating collagen deposition on the wound bed.

The review has allowed for a randomized (38), controlled blind experiment: 35 healthy patients, non-smokers, aged 70 years or older, without gender distinction were examined. Each patient was administered two catheters in polytetrafluorotheyelen (PTFE) under the skin, in the deltoid area. Throughout the duration of the study, i.e. two weeks, 18 subjects were randomly assigned 1g of arginine, 3g of HMB and 14g of glutamine. Instead, the first (control) group, consisting of 17 patients, a mixture of non-essential amino acids: isoazotate and isocaloric was administered.

Table 3. Components that support processes involved in the wound healing

ARGININE	**GLUTAMINE**	**HMB** *(metabolita of leucin)*
• Improves healing of wounds (31, 13) • Stimulates synthesis and collagen deposition (32); • Supports protein synthesis (32); • Supports immune function (33).	• Improves the healing of skin wounds by stimulating collagen synthesis (32); • Supports protein synthesis (33; 13); • Maintains intestinal integrity and supports immune function (34).	• Decreases muscle protein degradation (35); • Increases urea retention, indication of protein metabolism (36); • It has anti inflammatory effects (37).

The catheters were removed at 7 and 14 days from the implant and analyzed to determine the levels of hydroxyproline (OHP, an index of collagen accumulation) and nitrogen beta-amine (an index of protein synthesis) (38). Another randomized, double-blind controlled study (39), taken in to consideration investigates whether the combination of arginine, HMB and glutamine (HMB / Arg / Gln) may alter the course of muscle mass loss in patients with acquired immunodeficiency syndrome (*AIDS*). The recruited subjects, 54 male and 14 female, all with full-blown AIDS and > 5% weight loss in the previous three months.

The study was conducted by randomizing patients for the administering of a blend of 3g of HMB, 14g of arginine and 14g of glutamine administered twice a day or of the control mixture containing malt dextrin. At eight weeks a significantly higher weight gain ($p = 0.009$) in the HMB / Arg / Gln group consisting of 22 subjects compared to the control group who received a placebo consisting of 21 subjects was registered (39). The analysis of the results showed that integration with arginine, HMB and glutamine caused a significant increase in arginine and ornithine levels.

Regarding collagen content (OHP), however, at a distance of one week, it was not possible to achieve any effect, while at two weeks, a significant increase was achieved; ($p < 0.03$) greater than collagen 72.2 nmol / cm of plant in the first group to which the arginine / HMB / glutamine mixture was administered, compared to 43.2 nmol / cm of the control group to which a placebo was administered. In healthy elderly subjects, collagen synthesis is significantly increased by the administration of a mixture of arginine, HMB and glutamine. At dosed doses, the mixture constitutes a safe nutritional product for better healing (40). The combination of HMB/Arg/Gln can significantly improve the course of lean mass loss in patients with related cachexia AIDS and can improve immune status in these patients (41).

Conclusions

The findings of the studies included in this review show the benefits of mixing components such as arginine, HMB and glutamine are highlighted on wound healing. The mixture is well tolerated and it has no toxic effects. Arginine and glutamine amino acids (*HMB, metabolite of amino acid leucine*) are the key ingredients of a single blend, favouring the preservation of proteins essential for resolution of the wounds (42). Despite efforts in preventing and treating malnutrition, the prevalence of disease-related malnutrition remains consistently (43). The healing of skin wounds requires the intervention of a multidisciplinary team that oversees nutrition, surgical procedures, wound healing and dressing, and overall patient health. An integral part of the team is definitely the nurses who are responsible for managing the patient's nutrition (in collaboration with a specialized nutritionist) and wound management (44). The patient's state of nutrition therefore not only affects the risk of ulcer but also their evolution and severity (15, 45). Educating the patient to take the right dose of protein can help them achieve maximum diet compliance and improve clinical outcomes (19). There is therefore a need for a wound specialist nurse, by implementing the wound bed preparation and debridement, favours healing.

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Correspondence:
Marco Di Muzio
Department of Clinical and Molecular Medicine, Sapienza University of Rome 00185, Italy
E-mail: marco.dimuzio@uniroma1.it